41. (New) An isolated and purified nucleic acid which hybridizes, under stringent conditions comprising hybridization in aqueous solution containing 4-6X SSC at 65-68° C, or 42° C in 50% formamide, to the complement of a polynucleotide of SEQ ID NO:1, wherein the nucleic acid encodes a protein that stimulates ribosomal RNA transcription.

42. (New) An isolated and purified nucleic acid which encodes the rRNA transcription-stimulating protein encoded by the nucleic acid of claim 41;

43. (New) An isolated and purified nucleic acid which is the full length complement of the nucleic acid of claim 41.

44. (New) An isolated and purified nucleic acid which is the full length complement of the nucleic acid of claim 42.

REMARKS

Claims 1-38 are currently pending in the above-identified application. The Examiner has acknowledged Applicant's election with traverse of group 1, claims 1-5 and 7-19. Group III, claims 20-24, have been rejoined by the Examiner on reconsideration of the Request for Restriction. Claims 1-5 and 7-24 have therefore been examined on the merits. By this amendment, claims 1, 2, and 7 have been amended. Also, claims 25-38 have been canceled as directed to a non-elected invention without prejudice to prosecution of the subject matter encompassed by the claims in a related, co-pending application. Further, new claims 39-44 which recite particular embodiments of the claimed invention which were disclosed in the application as filed but not specifically claimed have been added. Support for the amended claims and newly added claims can be found throughout the specification and in particular on, for example, page 6, lines 21-24; page 7, lines 13-27; page 13, lines 28-30; page 15, lines 16-23; page 16, lines 7-18; page 27, lines 10-17; and page 69, claims 1 and 4. No new matter has been added by these amendments.

Claims 1, 2, and 7 have been amended to set forth the invention with greater particularity. In claims 1 and 7, the phrase "which Rrn3 polypeptide stimulates ribosomal RNA transcription" has been inserted following the phrase "wherein the Rrn3 polypeptide ...." to further clarify the polypeptide encoded by the polynucleotide hybridization substrate. The terminal phrase describing the Rrn3 polypeptide has been deleted. Because Applicants believe that these amendments merely clarify that which would be known to the skilled artisan reading the claim in light of the specification, Applicants believe that this amendment is not narrowing.

In addition, in claim 2, the phrase "genomic DNA, cDNA, mRNA or antisense RNA" has been amended to recite "genomic DNA, cDNA, or RNA." Applicants note that RNA, as understood by the skilled artisan and as further defined in the specification (*see, e.g.*, page 6, lines 9-12 and 21-24), can include any type of RNA such as both mRNA and antisense strands. Therefore, Applicants believe that this amendment is not narrowing.

Rejections Under 35 U.S.C. § 112, First Paragraph:

Claims 1, 2, 4, and 7-24 stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner believing the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner, citing *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), states that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." The Examiner goes on to allege that the specification does not describe the "common attributes or characteristics that identify members of the genus," stating that "because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen is insufficient to describe the genus."

Applicants respectfully traverse the instant rejection. Applicants respectfully remind the Examiner that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical characteristics, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.'" *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, 1613, 1616 (Fed. Cir. 2002) (adopting PTO's applicable standards and citing Written Description Guidelines, 66 Fed. Reg. 1099, 1106) (emphasis original). Thus, written descriptive support for a genus under § 112 may be shown not only by recitation of structural features, but by disclosure of functional characteristics common to members of the genus. Here, because there is a well-known correlation between hybridization properties of nucleic acids and their structure, *claims based on such hybridization properties are permissible where the hybridization substrate is adequately disclosed. Enzo*, 63 USPQ2d at 1616 (adopting PTO Guidelines with respect to functional claiming of biological

materials, including genus claims to nucleic acids based on hybridization properties, and stating that "functional claiming is permissible when the claimed material hybridizes to a disclosed substrate"); *see also* Synopsis of Application of Written Description Guidelines, at pages 35-37, (Example 9: Hybridization).

In view of these standards, Applicants believe that the claims as originally filed have sufficient written descriptive support in the specification because Applicants have provided disclosure of the complete RRN3 nucleic acid substrate and have claimed nucleic acids hybridizing to the substrate under highly stringent conditions. Further, without acquiescing to the remarks of the Examiner, Applicants have amended Claims 1 and 7 as set forth above to clarify the function of the protein encoded by the human RRN3 nucleotide substrate. Therefore, Claim 1 recites nucleic acids that hybridize, under specified conditions of 4-6x SSC at 65-68° C or 42° C in 50% formamide, to a polynucleotide that codes for human RRN3 polypeptide, or to the complement of the polynucleotide, "wherein the Rrn3 polypeptide, which Rrn3 polypeptide stimulates ribosomal RNA transcription, comprises the contiguous amino acid sequence of SEQ ID NO:2, or a fragment thereof." Applicants note that disclosure of the amino acid sequence of SEQ ID NO:2 constitutes adequate disclosure of all polynucleotides encoding SEQ ID NO:2, including fragments thereof, *see* 66 Fed. Reg. at 1111, n.57 (citing Federal Circuit cases). Further, the recited hybridization conditions were well-known in the art at the time of filing the present invention as highly stringent. *See, e.g.*, Synopsis of Application of Written Description Guidelines at page 35.

Thus, "the necessary common attribute" of members of the claimed genus is the ability to hybridize to the disclosed substrate, *i.e.*, the polynucleotide that codes for human *RRN3* polypeptide of SEQ ID NO:2, or fragments thereof, or to the complement of the polynucleotide, under the recited highly stringent conditions. Applicants respectfully note that hybridization properties of nucleic acids are highly predictable in the art. Because highly stringent conditions yield structurally similar DNAs, "a person of ordinary skill in the art *would not expect substantial variation among species* encompassed within the scope of the claims." *See Enzo*, 63 USPQ2d at 1615 (stating that

"genus claims to nucleic acids based on hybridization properties ... may be adequately described if they hybridize under highly stringent conditions to known sequences because *such conditions dictate that all species within the genus will be structurally similar*). Such predictability and skill in the art together with the recited highly stringent hybridization conditions are thus sufficient to determine that Applicant had "possession" of the claimed genus.

Accordingly, the specification as filed satisfies the written description requirement under 35 U.S.C. § 112, first paragraph. Written description is satisfied by disclosure of "sufficiently detailed, relevant identifying characteristics," including functional characteristics that are "coupled with a known or disclosed correlation between structure and function." As discussed above, hybridization properties of nucleic acids, particularly where hybridization is under highly stringent conditions, meets this threshold. Because the hybridization substrate is adequately disclosed as discussed above, the specification provides written descriptive support for the claimed invention as required under 35 U.S.C. § 112, first paragraph.

Therefore, for the reasons set forth above, Applicants believe that claims 1, 2, 4, and 7-24 are adequately described by the specification as filed. Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 2, 4, and 7-24 for lack of written description under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 101:

Claims 1-5, and 7-24 stand rejected under 35 U.S.C. §101, the Examiner believing that the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. The Examiner alleges that "the disclosure is not sufficient to determine what the biological function(s) of the human Rrn3 gene product is," stating that the rescuing of the lethal yeast Rrn3 null mutation by human Rrn3 does not tell how human Rrn3 works in the human body. The Examiner cites to the specification and other art for the asserted proposition that the function of Rrn3 is not known. The Examiner further apparently believes that the asserted utility for

hRrn3 is not specific, stating that "multiple transcription factors stimulate rRNA transcription" and that "human Rrn3's ability to stimulate rRNA transcription is not specific to Rrn3 protein." The Examiner also states that sequence similarity to yeast Rrn3 protein "does not necessarily mean that human Rrn3 has [the] same biological function to yeast Rrn3" and that "function cannot be predicted based solely on structural similarity."

Applicants respectfully traverse the instant rejection. First, Applicants respectfully disagree with the Examiner's rejection of the claims under 35 U.S.C. § 101 for alleged lack of either a credible, specific, or substantial asserted utility or a well established utility based on insufficiency of the yeast complementation assays and structural homology to yeast Rrn3 protein. The Examiner has concluded the utilities disclosed in the specification relating to activity of Rrn3 in rRNA transcription, are not credible. In this regard, Applicants respectfully note that a rejection for lack of utility is improper where an asserted utility is "believable based on the record or the nature of the invention." MPEP § 2107.02 at 2100-39. An applicant's assertion of utility "creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101" unless there is reason for one skilled in the art to question the objective truth of the stated utility. *Id.*, *citing In re Jolles*, 206 USPQ 885 (CCPA 1980); *In re Irons*, 144 USPQ 351 (CCPA 1965); *In re Langer*, 183 USPQ 288 (CCPA 1974); *In re Sichert*, 196 USPQ 209, 212-13 (CCPA 1977). The Court of Customs and Patent Appeals stated in the following in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented *must* be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter *unless* there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer, 183 USPQ at 297 (emphasis original), *followed by In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995). Thus, a "rigorous correlation" between the evidence and the

asserted utility "need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient." *Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996); *see also* MPEP § 2107.03 at 2100-43 (citing cases). To overcome the presumption of truth of Applicants' disclosed utility, the Examiner must establish that, more likely than not, one of ordinary skill in the art would doubt the truth of the statement of utility. *See In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

In the present case, Applicants' specification discloses, *inter alia*, that a nucleic acid of SEQ ID NO:1 complements the rrn3$^-$ null mutation in yeast (*see, e.g.*, page 65, lines 18-21) and further discloses that human Rrn3 protein having the amino acid sequence depicted as SEQ ID NO:2 is structurally similar to yeast Rrn3 (*see* page 14, lines 3-5). The skilled artisan would consider complementation of yeast null mutants by human genes as predictive of the biological function of the encoded gene product. This is particularly true where the gene of interest from a higher organism encodes a molecule with a function common to both yeast and the other higher organism. Further, the correlation is more predictive of the biological function where sequence similarity exists between the protein sequence encoded by the gene of yeast and the higher organism.

Rrn3 is involved in a biological function common to both yeast and higher organisms. In particular, Rrn3 is involved in rRNA transcription, a cell cycle function that is common to not only yeast and higher organisms, but to all cells including humans. Examples of disclosures demonstrating yeast complementation of human genes encoding molecules involved in processes common to yeast and human cells include, for example, Lee and Nurse, *Nature* 327:31-35 (1987) (concluding, based on yeast complementation and similarity of predicted protein sequence between yeast and human cdc2, that "elements of mechanism by which the cell cycle is controlled are likely to be conserved between yeast and human" (see Abstract)); Tanaka *et al.*, *J. Biochem.* (Tokyo) 104:477-480 (1988) (finding degrees of complementation of yeast CYC1 deficiency by mutated human cytochrome c genes to be predictive of relative importance of particular conserved residues (see Abstract)); Hoshino *et al.*, *EMBO J.* 8:3807-14 (1989) (describing

functional characterization of human GST1-Hs, a human homologue of yeast GST1 encoding a GTP-binding protein, by complementation of yeast gst1 null mutant). Therefore, yeast complementation is routinely used to ascertain the function of genes in higher organisms, including humans, and when combined with structural homology would be sufficient to demonstrate utility to the skilled artisan. Based on the evidence presented in the specification, including yeast complementation and homology to yeast Rrn3, a person of ordinary skill in the art would regard as believable Applicants' disclosure of human Rrn3 as a factor regulating rRNA transcription and, thus, the disclosed utilities relating to the disclosed biological activity.

Moreover, Applicants believe that the Examiner has not met the requisite burden for showing a *prima facie* lack of utility. Applicants respectfully disagree with the Examiner' s reliance on Scott *et al.*, *Nature Genetics*, 21:440-443 (1999), which the Examiner cites for "the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function." In contrast to the data in Scott *et al.*, the yeast complementation provides just such confirmation. Scott *et al.* were unable to detect a sulfate transport activity, postulated based on homology to other known sulfate transporters, for a human protein (pendrin, encoded by the gene *PDS*) following introduction of the *PDS* gene into *Xenopus* oocytes and Sf9 cells. Applicants believe Scott *et al.* to be irrelevant to how one skilled in the art would view Applicant's disclosure because the reference only pertains to prediction of function based on sequence similarity and a ***failure to detect*** the postulated activity. In the present case, Applicants have shown both sequence homology with a known protein rRNA transcription factor ***and positive data showing activity*** as a rRNA transcription factor.

Applicants similarly disagree with the Examiner's reliance on Skolnick *et al.*, *Trends in Biotech.* 18:34-39 (2000); Bork, *Genome Research* 10:398-400 (2000); Doerks *et al.*; *Trends in Genetics* 14:248-250 (1998); Smith *et al.*, *Nature Biotechnology* 15:1222-1223 (1997); Brenner, *Trends in Genetics* 15:132-133 (1999); and Bowie *et al.*, *Science* 247:1306-1310 (1990). The Examiner cites these references collectively for the

general assertion that "function cannot be predicted based solely on structural similarity to a protein found in the sequence databases." As indicated above, and assuming *arguendo* that sequence similarity alone is insufficient to predict biological function, Applicants respectfully note that the specification demonstrates biological activity of the human Rrn3 as a rRNA transcription factor by yeast complementation and thus shows more than just sequence homology with a known Rrn3 protein. Therefore, Applicant's disclosure of utility is not based "solely" on sequence similarity and the respective references cited by the Examiner in this regard are irrelevant.

In addition, Applicants disagree with the Examiner that the structural homology of the disclosed human Rrn3 protein to known rRNA transcription factors is alone insufficient to support the disclosed utility. Successful demonstration in the art of a utility for known compositions is evidence that one skilled in the art would believe that structurally similar compositions have the utility. *In re Brana*, 34 USPQ2d1436, 1442 (Fed. Cir. 1995).

Applicants also respectfully disagree with the Examiner's reliance on the statements cited in the specification at page 2, lines 24 and 25, and Moorefield *et al.*, *Proc. Natl. Acad. Sci. USA* 97:4724-4729 (2000) for the allegation that the function of Rrn3 protein is not known. The specification states that "[a]lthough the *specific* function of Rrn3 polypeptide is as yet unknown, it is essential for rRNA gene transcription in vivo *and* in vitro, and it may be required to mediate productive interactions of pol I with the preinitiation complex" (*see* page 2, lines 24-27) (emphasis added). Thus, the statement relied on by the Examiner refers only to the "specific" mechanism of action of Rrn3, *i.e.*, how the protein works to achieve its function in stimulating rRNA gene transcription through, *e.g.*, interactions with other specific factors (*i.e.*, mechanism of action). Similarly, Moorefield *et al.* also disclose the particular biological activity of hRrn3 in transcription initiation and merely state that specific interactions with other initiation factors, which again pertain only to Rrn3's "mechanism of action," have yet to be fully characterized (*see, e.g.*, page 4728, second column). Applicants note that "it is not a

requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman v. Quigg*, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989).

In addition, to the extent that the Examiner believes that no specific utility has been asserted because human Rrn3's ability to stimulate rRNA transcription is allegedly "not specific to Rrn3 protein," Applicants must respectfully disagree. Applicants believe that Milkereit *et al.*, *EMBO J.* 17:3692-3703 (1998), cited by Examiner for the assertion that "multiple transcription factors stimulate rRNA transcription," is insufficient to refute the specificity of Applicant's disclosed utilities since it is irrelevant whether another composition might have a similar activity. "Specific utility" under 35 U.S.C. § 101 simply requires that the asserted utility be "*specific* to the subject matter claimed" as opposed to a "*general* utility that would be applicable to the broad class of invention." Revised Interim Utility Guidelines Training Materials, at 5; *see also* MPEP § 2107.02 at 2100-38 (disclosure that identifies a particular biological activity and a use in a particular application contains an assertion of specific utility). Here, the claimed subject matter relates to nucleic acids encoding Rrn3 polypeptides, the polypeptides having a specified biological activity, *i.e.*, stimulation of ribosomal RNA transcription. The broad class of the claimed invention includes nucleic acids and polypeptides generally. Therefore, while asserted utilities that are generally applicable to any nucleic acid and or polypeptide (*e.g.*, use as probes for unspecified targets or use as food supplements) would not be specific, *see* Revised Interim Utility Guidelines Training Materials, at 7, *any asserted utility that relates to the biological activity of Rrn3 in stimulating ribosomal RNA transcription would be a "specific" utility* under § 101.

In light of the above, Applicants respectfully disagree with the Examiner's characterization of the asserted utilities referred to in the Office Action. Further, Applicants note that the Examiner cites only to portions of the specification disclosing utilities that relate to the treatment, prevention, diagnosis, and screening of diseases involving hyperproliferation and hypoproliferation and to screening for agonists and antagonists for agents that are therapeutically effective as anti-proliferative agents. The

Examiner goes on to allege that such utilities are not specific, stating that involvement in a specific proliferative disorder is not established.

Applicants believe that the disclosed utilities are specific as required under 35 U.S.C. § 101. Applicants initially wish to point out that, for purposes of satisfying the utility requirement under 35 U.S.C. § 101, it is not required that Applicants "establish" involvement in a disease. Whether a claimed composition *in fact* possesses a specific biological property is not the issue under 35 U.S.C. § 101. *In re Kirk*, 153 USPQ 48, 52 (CCPA 1967). Rather, it is the disclosed utility that is determinative, *id.*, and the question is whether there is a "reasonable correlation" between the disclosed utility and the evidence of record, *Fujikawa*, 39 USPQ2d at 1900. In the present case, Applicants have disclosed utilities relating, *inter alia*, to the treatment, prevention, diagnosis, and screening of hyperproliferative and hypoproliferative disorders, including, for example, "malignancies, premalignant conditions (*e.g.*, hyperplasia, metaplasia, dysplasia), benign tumors, ... and the like" as well as cardiac disease. (Specification at page 37, lines 23-28.) These diseases are specific and the asserted uses for, *e.g.*, treatment, prevention, screening, and diagnosis of such diseases are likewise "specific" under 35 U.S.C. § 101 because they relate specifically to the disclosed activity of Rrn3 polypeptide in rRNA transcription and regulation of cell proliferation.

In this regard, Applicants believe Schnapp *et al.*, *EMBO J.* 9:2857-2863 (1990), to be irrelevant to "specific" utility. The Examiner cites to Schnapp *et al.* as stating that "'regulation of cell proliferation is a complex process' involving a lot of proteins." However, as stated above, "specific" in the context of utility means "relating specifically to the claimed subject matter" rather than the general class of invention. Thus, whether a disclosed use is "specific" does not depend on any "complexity" of biological processes in which the subject matter is involved, but only on whether the disclosed use relates to the biological processes.

Moreover, Applicants respectfully note that the Examiner has not addressed Applicants' disclosed use for *RRN3* nucleic acids and Rrn3 polypeptides for screening of antifungal agents in isogenic yeast strains to identify agonist or antagonists

of Rrn3 that are specific for one eukaryotic *RRN3* nucleic acid or Rrn3 polypeptide, but not another *RRN3* nucleic acid or Rrn3 polypeptide. (*See, e.g.*, specification at page 55, lines 7-21.) Applicants believe that, in addition to the specific uses discussed above, the disclosed use for the claimed *RRN3* nucleic acids and Rrn3 polypeptides in screening for antifungal agents in isogenic yeast strains, in particular, to be specific, credible, and substantial.

For the reasons set forth above, Applicants believe that the specification as filed satisfies the utility requirement. Applicants therefore, respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 2, 4, and 7-24 under 35 U.S.C. § 101.

Rejections Under 35 U.S.C. § 112, First Paragraph:

Claims 1, 2, 4, and 7-24 stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner believing that the specification, while being enabling for how to make the DNA of SEQ ID:1 for encoding full-length human Rrn protein "with potential" to stimulate ribosomal RNA transcription, does not reasonably provide enablement for how to use SEQ ID NO:1 or how to make and use any other DNA molecules that hybridize to SEQ ID NO:1 or fragment of SEQ ID NO:1. The Examiner asserts that the specification teaches SEQ ID NO:1 to produce SEQ ID NO:2 "that might" stimulate transcription of ribosomal RNA, further alleging that the specification "does not describe [that] the protein indeed stimulate[s] rRNA transcription but only speculates the activity." The Examiner believes that the specification does not provide guidance for how to use the nucleic acids encompassed by claims 1, 2, 4, and 7-24.

Applicants respectfully traverse the instant rejection. In particular, Applicants respectfully disagree with the Examiner's allegation that the specification merely "speculates the activity" of hRrn3. Applicants initially note that this aspect of the Examiner's rejection relates to the "how to use" prong of 35 U.S.C. § 112, which incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose a practical utility for the invention. *In re Ziegler*, 26 USPQ2d 1600, 1603 (Fed. Cir. 1993). In this regard and as discussed above, Applicants respectfully submit that the

specification adequately discloses a specific, credible, and substantial utility as required under 35 U.S.C. § 101.

Briefly, Applicants again note that the disclosed utility for a claimed invention is sufficient where it is "believable based on the record or the nature of the invention." MPEP § 2107.02 at 2100-39. All that is required is that the evidence of record have a "reasonable correlation" with the asserted utility. *E.g., Fujikawa*, 39 USPQ2d at 1900. As discussed above, the specification provides sufficient evidence to establish a reasonable correlation with a disclosed utility relating to Rrn3 activity, *e.g.*, the modulation of rRNA transcription, such that a person of ordinary skill in the art would find the disclosed uses credible. The specification provides, *inter alia* and in addition to structural homology with known rRNA transcription factors, a direct demonstration of the biological activity of hRrn3 as a rRNA transcription factor (*see, e.g.*, page 65, lines 14-21). Thus, Applicants believe that the specification does not "speculate" but instead demonstrates the ability of hRrn3 to stimulate rRNA transcription.

Further, whether a use is enabled is analyzed in view of the practical utility disclosed in the specification. *See Cross et al. v. Iizuka et al.*, 224 USPQ 739, 748 (Fed. Cir. 1985); *accord In re Kirk*, 153 USPQ 48, 52 (CCPA 1967). In addition, the "how to use" prong of enablement under § 112, because it incorporates the standards for utility under § 101, only requires enablement of one disclosed use. *See, e.g., Carl Zeiss Stiftung v. Renishaw plc*, 20 USPQ2d 1094, 1100 (1991).

In this case, as discussed above, Applicants believe that the utilities disclosed in the specification satisfy the utility requirement under 35 U.S.C. § 101. The specification discloses, for example, at least the use of the claimed nucleotides for the screening of antifungal agents in isogenic yeast strains to identify agonists or antagonists of Rrn3 that are specific for one eukaryotic *RRN3* nucleic acid or Rrn3 polypeptide, but not another *RRN3* nucleic acid or Rrn3 polypeptide. (*See, e.g.*, page 55, lines 7-21.) Applicants do not believe that this disclosed utility has been addressed in the Examiner's discussion under § 101. As stated above, and in light of the above remarks regarding disclosure of utility under 35 U.S.C. § 101, Applicants believe that each use disclosed in

the present application, including the use for screening of antifungal agents, is specific, credible, and substantial. To the extent that the Examiner has not specifically applied the standards of the "how to use" requirement of 35 U.S.C. § 112 to the uses disclosed in the specification, including the use for screening in isogenic yeast strains, Applicants believe that the Examiner has not made a *prima facie* case for lack of enablement under 35 U.S.C. § 112.

Moreover, Applicants believe that the specification enables those skilled in the art "how to use" the claimed invention. Applicants respectfully note that the scope of enablement need "only bear a 'reasonable correlation' to the scope of the claims." MPEP § 2164.08 at 2100-186, *citing In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Accordingly, everything necessary to practice the invention need not be disclosed; rather, "all that is necessary is that one skilled in the art be able to practice the invention, given the level of knowledge and skill in the art." MPEP § 2164.08 at 2100-186. In addition, the presence of inoperative embodiments within the scope of a claim does not render a claim non-enabled where the skilled artisan "could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with the expenditure of no more effort than is normally required in the art." *Id.* at (b), 2100-188, *citing Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984). Also, "[t]he determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In light of the above, Applicants respectfully disagree with the Examiner's allegation that the claims are non-enabled merely because certain modifications of a peptide or protein structure can affect biological activity. "It is not a function of the claims to exclude possible inoperative substances." *Atlas Powder*, 224 USPQ at 414. The question, as indicated above, is whether the skilled artisan would be able to determine, with no more effort than normally required in the art, which hybridizing sequences encode a Rrn3 polypeptide with the ability to modulate rRNA transcription. In

this regard, Applicants first note that, in addition to the similarity of primary structure, as dictated by highly stringent conditions, of nucleic acid sequences hybridizing to the substrate sequence, *i.e.*, SEQ ID NO:1 or sequences encoding the Rrn3 polypeptide of SEQ ID NO:2, methods of secondary structural analysis were well known in the art at the time the application was filed (*see, e.g.*, methods described in specification at page 31, lines 4-18). Moreover, Applicants respectfully disagree with the Examiner to the extent the Examiner suggests, in citing to Bowie *et al.*, Burgess *et al.*, and Lazar *et al.*, that the artisan is constrained to determinations based on structural similarity alone. As of the effective filing date, routine methods for assaying the ability of an Rrn3 polypeptide to stimulate rRNA transcription were well-known in the art (*see, e.g.*, specification at page 35 , lines 12-24 (describing method of Klein and Grummt, *Proc. Natl. Acad. Sci. USA* 96:6096-6101, 1999). In addition, the specification describes a routine method for determining Rrn3 biological activity of a nucleotide sequence by complementation of a yeast rrn3 null mutant. (*See, e.g.*, page 55, lines 7-11, and Examples 7 and 8, pages 64-67.)

Thus, because the nucleotide sequences disclosed in the specification, in conjunction with the recited hybridization conditions, limit the structure of any effective Rrn3 sequence, and because there were routine art-recognized and disclosed methods for determining operative embodiments within the scope of the claims, the claims are adequately enabled as required under 35 U.S.C. § 112, first paragraph, for how to make and use the full scope of the claimed invention.

In light of the above remarks, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 2, 4, and 7-24 for lack of enablement under 35 U.S.C. § 112, first paragraph.

Claims 1-5 and 7-24 also stand rejected under 35 U.S.C. §112, first paragraph, the Examiner believing that the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility, and that one skilled in the art would not know how to use the claimed invention.

Applicants respectfully traverse the instant rejection. For the reasons stated above in response to the Examiner's rejections under 35 U.S.C. §§101 and 112, first paragraph, Applicants believe that the full scope of the claims are enabled for how to use the claimed invention.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-5 and 7-24 for lack of enablement under the "how to use" prong of 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 10 January 2003

By: Brian W. Poor
Brian W. Poor
Reg. No. 32,928

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 206-467-9600
Fax: 415-576-0300
BWP:jms
SE 5014593 v5

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please delete the paragraph beginning at page 12, line 13, and insert the following:

The term "immunologically cross-reactive" means that a polypeptide, fragment, derivative or analog is capable of competitively inhibiting the binding of an antibody to its antigen.

Please delete the paragraph beginning at page 22, line 31, and insert the following:

Any of the methods previously described for the insertion of DNA fragments into a vector can be used to construct expression vectors containing a chimeric gene consisting of appropriate transcriptional/translational control signals and the polypeptide coding sequences. These methods include *in vitro* recombinant DNA and synthetic techniques and *in vivo* recombinants (genetic recombination). Expression of nucleic acid sequences encoding a Rrn3 polypeptide or fragment can be regulated by a second nucleic acid sequence so that the Rrn3 polypeptide or fragment is expressed in a host transformed with the recombinant DNA molecule. For example, expression of a Rrn3 polypeptide can be controlled by any promoter/enhancer element known in the art. Promoters which can be used to control *RRN3* gene expression include, but are not limited to, the SV40 early promoter region (Benoist and Chambon, *Nature* 290:304-10 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al.*, *Cell* 22:787-97 (1980)), the herpes thymidine kinase promoter (Wagner *et al.*, *Proc. Natl. Acad. Sci. USA* 78:1441-45 (1981)), the regulatory sequences of the metallothionein gene (Brinster *et al.*, *Nature* 296:39-42 (1982)), prokaryotic

expression vectors such as the β-lactamase promoter (Villa-Komaroff *et al.*, *Proc. Natl. Acad. Sci. USA* 75:3727-31 (1978)) or the *tac* promoter (deBoer *et al.*, *Proc.* [*Nalt.*]*Natl. Acad. Sci. USA* 80:21-25 (1983)), plant expression vectors including the cauliflower mosaic virus 35S RNA promoter (Gardner *et al.*, *Nucl. Acids Res.* 9:2871-88 (1981)), and the promoter of the photosynthetic enzyme ribulose biphosphate carboxylase (Herrera-Estrella *et al.*, *Nature* 310:115-20 (1984)), promoter elements from yeast or other fungi such as the *Gal7* and *Gal4* promoters, the ADH (alcohol dehydrogenase) promoter, the PGK (phosphoglycerol kinase) promoter, the alkaline phosphatase promoter, and the like.

Please delete the paragraph beginning at page 60, line 24, and insert the following:

A recently reported human EST (gb|AW239267, which corresponds to nucleotides 1661 to 2068 of SEQ ID NO:1) encodes an additional 3' portion of the human *RRN3* cDNA. The full length cDNA thus encodes a polypeptide of 651 [animo]amino acids with a predicted molecular mass of 74 kD, which is similar to that of TIF-IA. The sequence of the human *RRN3* open reading frame has been deposited in the GenBank database (Accession No. AF227156).

Please delete the paragraph beginning at page 62, line 3, and insert the following:

To confirm that the human cDNA encodes a polypeptide which is related to yeast Rrn3, the human and yeast *RRN3* cDNAs were expressed in *E. coli* as 6-His fusion proteins and subjected to Western blot analysis. Full length yeast or human *RRN3* coding sequences were subcloned into pRSET vector (Invitrogen) to generate 6-His [togged]tagged proteins for expression in *E. coli*.

IN THE CLAIMS:

1. (Amended) An isolated and purified nucleic acid which hybridizes under stringent conditions comprising hybridization in aqueous solution containing 4-6x SSC at 65-68° C, or 42° C in 50% formamide, to a polynucleotide that codes for human RRN3 polypeptide, or the full length complement of the polynucleotide, wherein the Rrn3 polypeptide, which Rrn3 polypeptide stimulates ribosomal RNA transcription, comprises the contiguous amino acid sequence of SEQ ID NO:2, or a fragment thereof[, which Rrn3 polypeptide or fragment thereof stimulates ribosomal RNA transcription.]

2. (Amended) The nucleic acid of claim 1, which is genomic DNA, cDNA, or [m]RNA [or antisense RNA].

7. (Amended) An expression construct comprising the following operably linked elements:

a transcriptional promoter;

a RRN3 polynucleotide which hybridizes under stringent conditions comprising hybridization in aqueous solution containing 4-6x SSC at 65-68° C, or 42° C in 50% formamide, to a polynucleotide encoding a Rrn3 polypeptide or the full length complement of the polynucleotide, wherein the Rrn3 polypeptide, which Rrn3 polypeptide stimulates ribosomal RNA transcription, comprises the contiguous amino acid sequence of SEQ ID NO:2 or a fragment thereof[, which Rrn3 polypeptide or fragment thereof stimulates rRNA transcription]; and

a transcriptional terminator.